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| BERTAGNA, ANGELA MARIE | |
| **ART UNIT** | **PAPER NUMBER** |
| 1637 | |

DATE MAILED: 08/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 10/621,693 | Applicant(s) BUSSELL, STUART | |
|---|---|---|---|
| | Examiner Angela Bertagna | Art Unit 1637 | |

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on 26 June 2006.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 133-175 is/are pending in the application.

4a) Of the above claim(s) 151,155,157,159,161,167,168,170,172 and 175 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 133-150,152-154,156,158,160,162-166,169,171,173 and 174 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 06 November 2003 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 7/2/2004.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

1. Applicant's election without traverse of Group I, claims 133-150, 152-154, 156, 158, 160, 162-166, 169, 171, 173, and 174, in the reply filed on June 26, 2006 is acknowledged.

Claims 151, 155, 157, 159, 161, 167-168, 170, 172, and 175 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on June 26, 2006.

### *Specification*

2. The disclosure is objected to because of the following informalities: Figures 12 and 19 and also Table 1 on page 46 contain nucleic acid sequences greater than 10 nucleotides in length that are not identified by the appropriate SEQ ID Nos. See MPEP 2422.02.

Appropriate correction is required.

### *Claim Rejections - 35 USC § 102*

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 133-145, 147-150, 152-154, 156, 158, 160, 162, 164-166, 169, 173, and 174 are rejected under 35 U.S.C. 102(b) as being anticipated by Elmorjani et al. (Biochemical and Biophysical Research Communications (1997) 239: 240-246; cited in IDS).

The instant claims are drawn to a multimer assembly of DNA comprising at least one amplification cassette encoding a protein or peptide of interest flanked by 5' and 3' restriction sites and further comprising linkers between the monomer units.

Regarding claims 133 and 136-138, Elmorjani teaches a multimer assembly of DNA sequences (see page 243, column 1 and also Figure 1) comprising:

(a) at least one amplification cassette, wherein said at least one amplification cassette comprises at least one monomer sequence whose polymerization is desired (Fig. 1 the ds oligonucleotide encoding the PQQPY pentapeptide), further wherein said at least one amplification cassette comprises a 5' restriction pair member at its 5' terminus and a 3' restriction pair member at its 3' terminus (Figure 1A, the EcoRI and HindIII sites, for example)

(b) and at least one of the following:

(b1) at least one 3'-terminal cassette, wherein said 3'-terminal cassette comprises at least one 3' specific sequence and a 5' restriction pair member site that can be fused to a 3' restriction pair member site of at least one of said at least one amplification cassette (Figure 1; the 3' terminal cassette results from digestion with EcoRI & SnaBI)

(b2) at least one 5'-terminal cassette, wherein said 5'-terminal cassette comprises at least one 5' specific sequence and a 3' restriction pair member site that can be fused to a 5' restriction pair member site of at least one of said at least one amplification cassette (Figure 1; the 5' terminal cassette results from digestion with EcoRI & StuI).

See also page 243, column 1 for a description of the amplification cassette depicted in Figure 1.

Regarding claim 134, Elmorjani teaches that the amplification cassette is at least two amplification cassettes (see Figure 1 and page 243, column 1, where Elmorjani teaches duplication of the PQQPY module to create an amplification cassette containing 8, 16, and 32 copies of the pentapeptide).

Regarding claim 135, Elmorjani teaches that the amplification cassettes are fused at restriction pair member partners (see Figure 1 and page 243, column 1).

Regarding claim 139, the multimer assembly taught by Elmorjani comprises 5' and 3' restriction pair member sites that are ligation-compatible non-regenerable blunt end restriction sites (see Figure 1, where the StuI and SnaB sites on the 5' and 3' cassette are non-regenerable blunt ended sites that are ligated together; see also page 243, column 1).

Regarding claims 140-142, Elmorjani teaches that the 5'-terminal cassette and 3'-terminal cassettes further comprise at least a portion of said monomer sequence (see Figure 1 and page 243, col. 1, where Elmorjani teaches that the 5'-terminal cassette and 3'-terminal cassettes comprise the entire monomer sequence – the pentapeptide PQQPY)

Regarding claims 143 and 144, Elmorjani teaches that the multimer assembly further comprises at least one linker and that the linker comprises at least one restriction pair member (see Figure 1, where the linker comprises the oligonucleotide sequence encoding the linker MVR, noting that the linker includes an EcoRI and NcoI site).

Regarding claim 145, Elmorjani teaches that the monomer sequence encodes a peptide of interest (Figure 1 and page 243, col. 1 – the PQQPY pentapeptide).

Regarding claims 147 and 148, Elmorjani teaches an amplification cassette comprising a 5' segment of a monomer sequence (the EcoRI/StuI fragment) and a 3' segment of a monomer sequence (the EcoRI/SnaBI fragment) that together comprise the sequence of a complete monomer (each fragment comprises the complete monomer; therefore, the ligated fragments comprise the whole monomer), wherein the 5' segment is positioned 3' of the 3' segment (the PQQPY portion of the 5' fragment is 3' of the EcoRI/SnaBI fragment upon ligation – see Fig. 1), and further wherein the 5' terminus of the 3' segment is a 5' restriction pair member (the EcoRI/SnaBI fragment contains a 5' EcoRI site) and the 3' terminus of the 5' segment is a 3' restriction pair member (the StuI site is located on the 3'terminus of the 5' fragment).

Regarding claim 149, the multimer assembly of Elmorjani comprises a linker positioned between the 5' segment and the 3' segment (see Figure 1, where the oligonucleotide encoding the MVR peptide is the linker).

Regarding claim 150, Elmorjani teaches that the multimer assembly of claim 133 comprises a first cassette and a second cassette (each cassette encoding the pentapeptide PQQPY; see Fig. 1 & p. 243), wherein when said first cassette comprises a 5'-terminal cassette (see Fig. 1), the second cassette comprises an amplification cassette (see Fig. 1) and when the first cassette comprises a 3'-terminal cassette, said second cassette comprises an amplification cassette. It is noted that the designations "first cassette" and "second cassette" are arbitrary, and therefore, either the 5'-terminal or 3'-terminal cassette taught by Elmorjani may be considered the first or second cassette.

Regarding claim 152, Elmorjani teaches a multimer cassette made by a process comprising the following steps: digesting the first and second cassettes at the 5' and 3' restriction

sites, ligating the fragments to generate a multimer assembly and screening for the correct orientation (see Figure 1 and page 243, col. 1).

Regarding claims 153 and 169, Elmorjani teaches that at least one of the cassettes comprises one or more flanking restriction sites (see Figure 1, where the cassettes contain flanking EcoRI/StuI sites (5'-terminal) and SnaBI/HindIII sites (3'-terminal)).

Regarding claim 154, Elmorjani teaches that the 5'-terminal and 3'-terminal cassettes have the same insertion restriction site (Fig. 1 and page 243, col. 1, the EcoRI site).

Regarding claim 156, Elmorjani teaches a multimer cassette made by a process comprising the following steps: digesting two cassettes each containing a flanking restriction site that is ligation-compatible with the restriction site on the other cassette and ligating the resulting fragments to generate a multimer cassette (see Figure 1 and page 243, col. 1, where the flanking, compatible site is the EcoRI site in the two cassettes).

Regarding claim 158, Elmorjani teaches an insertion cassette made by a process comprising the following steps: (a) providing a 5' and 3'terminal cassette both having a flanking restriction site distinct from the insertion restriction site (Fig. 1 the SnaBI and StuI sites in the 5' and 3' cassettes) and that are ligation-compatible with one another (p. 243 and Fig. 1 teach that these blunt sites are ligated together), (b) digesting the 5' and 3' cassettes at the insertion and flanking sites (Figure 1 and p. 243), and (c) ligating the first and second fragments resulting from step (b) to generate an insertion cassette (Figure 1 and p. 243).

Regarding claim 160, Elmorjani teaches a multimer cassette made by a process comprising the following steps: (a) digesting the insertion cassette at the restriction pair member sites and isolating a fragment containing the insert cassette, (b) digesting the amplification

cassette at its restriction pair sites and isolating a second fragment containing the amplification cassette, (c) ligating the fragments to generate multimer cassettes, and (d) testing for correct orientation. Figure 1 and page 243, col. 1 of Elmorjani teach that the process to generate the first insertion cassette is cycled multiple times to generate multimer cassettes comprising 8, 16, and 32 copies of the PQQPY pentapeptide. The insertion cassette corresponds to the fragment isolated by the EcoRI/SnaBI digestion and the amplification cassette corresponds to the fragment isolated from the EcoRI/StuI digestion.

Regarding claim 162, Elmorjani teaches a multimer cassette made by a process comprising the following steps (see Figure 1 and page 243, col. 1): (a) digesting and isolating the resulting fragment of an amplification cassette comprising a restriction site that is ligation-compatible with the insertion restriction site of the insertion cassette (the fragment resulting from the EcoRI/StuI digestion contains the ligation-compatible EcoRI site), (b) digesting the insertion cassette at the insertion restriction site (EcoRI) and the restriction pair member partner (StuI) to the amplification cassette's restriction pair member (SnaBI) and isolating the second fragment (Fig. 1 and p. 243), (c) ligating the first and second fragment to generate a multimer precursor (Fig. 1) and (d) digesting the precursor at both restriction sites and ligating it with itself to obtain a multimer cassette (see Figure 1 where Elmorjani teaches cycling of the process).

Regarding claim 164, Elmorjani teaches that the multimer assembly further includes a linker sequence adjacent to the monomer sequence of the amplification cassette (see Fig. 1, where the linker is the oligonucleotide sequence encoding the MVR peptide).

Regarding claims 165, 166, 173, and 174, Elmorjani teaches a vector comprising the multimer assembly of claim 133 (Fig. 1 and p. 243, col. 1) and also a host cell comprising the vector (p. 243, col. 1, where the vector was transformed into E. coli).

5. Claims 133-138, 140-146, 150, 152-154, 156, 164-166, and 169 are rejected under 35 U.S.C. 102(b) as being anticipated by Hallewell et al. (USPN 5,084,390; cited in IDS).

The instant claims are drawn to a multimer assembly of DNA comprising at least one amplification cassette encoding a protein or peptide of interest flanked by 5' and 3' restriction sites and further comprising linkers between the monomer units.

Regarding claims 133 and 136-138, Hallewell teaches a multimer assembly of DNA sequences (see Figure 2 and column 5, lines 6-46) comprising:

(a) at least one amplification cassette, wherein said at least one amplification cassette comprises at least one monomer sequence whose polymerization is desired (Fig. 2 the SOD monomer sequence in pSODCF1), further wherein said at least one amplification cassette comprises a 5' restriction pair member at its 5' terminus and a 3' restriction pair member at its 3' terminus (Figure 2, the BamHI and EcoRI sites)

(b) and at least one of the following:

(b1) at least one 3'-terminal cassette, wherein said 3'-terminal cassette comprises at least one 3' specific sequence and a 5' restriction pair member site that can be fused to a 3' restriction pair member site of at least one of said at least one amplification cassette (Figure 2; the 3' terminal cassette results from digestion of pSODNcoI with NcoI & EcoRI followed by ligation to the hinge linker. This construct contains a 5' restriction

site (BamHI) that can be fused to the BamHI site present in the amplification cassette of step a – see column 5, lines 31-46)

(b2) at least one 5'-terminal cassette, wherein said 5'-terminal cassette comprises at least one 5' specific sequence and a 3' restriction pair member site that can be fused to a 5' restriction pair member site of at least one of said at least one amplification cassette (Figure 2; the 5' terminal cassette results from digestion with BamHI and EcoRI).

Regarding claim 134, Hallewell teaches that the amplification cassette is at least two amplification cassettes (see for example, claim 3, column 10, lines 58-59, where 2-10 monomer units are taught).

Regarding claim 135, Hallewell teaches that the amplification cassettes are fused at restriction pair member partners (see Figure 2).

Regarding claims 140-142, Hallewell teaches that the 5'-terminal cassette and 3'-terminal cassettes further comprise at least a portion of said monomer sequence (see Figure 2, where Hallewell teaches that the 5'-terminal cassette and 3'-terminal cassettes comprise the entire monomer sequence – the hSOD coding sequence)

Regarding claims 143 and 144, Hallewell teaches that the multimer assembly further comprises at least one linker and that the linker comprises at least one restriction pair member (see Figure 2, where the 3'terminal cassette is ligated to the hinge linker; see also column 5, lines 6-45).

Regarding claim 145, Hallewell teaches that the monomer sequence encodes a protein of interest (see abstract and Figure 2, where the monomer sequence encodes the hSOD protein).

Regarding claim 146, Hallewell teaches that the 3' restriction pair member encodes a stop codon that is destroyed upon ligation to the 5' restriction pair member (see Figures 1 & 2, where the BamHI digestion and subsequent ligation removes the stop codon at the end of the hSOD sequence).

Regarding claim 150, Hallewell teaches that the multimer assembly of claim 133 comprises a first cassette and a second cassette (see Fig. 2 – the two hSOD cassettes), wherein when said first cassette comprises a 5'-terminal cassette (Fig. 2, the pSODCF1 portion), the second cassette comprises an amplification cassette (Fig. 2 the linker-ligated hSOD portion) and when the first cassette comprises a 3'-terminal cassette, said second cassette comprises an amplification cassette. It is noted that the designations "first cassette" and "second cassette" are arbitrary, and therefore, either the 5'-terminal or 3'-terminal cassette taught by Hallewell may be considered the first or second cassette.

Regarding claim 152, Hallewell teaches a multimer cassette made by a process comprising the following steps: digesting the first and second cassettes at the 5' and 3' restriction sites, ligating the fragments to generate a multimer assembly and screening for the correct orientation (see Figure 2 and column 5, lines 6-46).

Regarding claims 153 and 169, Hallewell teaches that at least one of the cassettes comprises one or more flanking restriction sites (see Figure 2, where the cassettes contain flanking BamHI and EcoRI sites).

Regarding claim 154, Hallewell teaches that the 5'-terminal and 3'-terminal cassettes have the same insertion restriction site (Figure 2 – the EcoRI site).

Regarding claim 156, Hallewell teaches a multimer cassette made by a process comprising the following steps: digesting two cassettes each containing a flanking restriction site that is ligation-compatible with the restriction site on the other cassette and ligating the resulting fragments to generate a multimer cassette (see Figure 2 column 5, lines 31-46, where the flanking, compatible site is the EcoRI site in the two cassettes).

Regarding claim 164, Hallewell teaches that the multimer assembly further includes a linker sequence adjacent to the monomer sequence of the amplification cassette (see Figure 2 and column 5, lines 31-46).

Regarding claims 165 and 166, Hallewell teaches a vector comprising the multimer assembly of claim 133 (Figure 2 – the pSODCF1/pSODHA1 construct) and also a host cell comprising the vector (see, for example, claim 19, column 12, lines 25-27).

### *Claim Rejections - 35 USC § 103*

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claim 163 is rejected under 35 U.S.C. 103(a) as being unpatentable over either of Elmorjani et al. (Biochemical and Biophysical Research Communications (1997) 239: 240-246) or Hallewell et al. (USPN 5,084,390) in view of Nissen et al. (US 2002/0142964 A1) and further in view of GenBank Accession No. E01123 (1997; see attached revision history).

Elmorjani and Hallewell separately teach the multimer assembly of claim 133, as discussed above.

Neither Elmorjani nor Hallewell teach construction of a multimer assembly using the hGH coding sequence as the monomer.

Nissen taught multimeric constructs of single-chain polypeptides comprising multiple copies of a cytokine including human growth hormone (see paragraphs 3, 19, and 66). Nissen further taught that a common problem with injected cytokines was insufficient half-life in the patient. Nissen taught that one method of overcoming the problem was to increase the size of the protein by generating multimeric constructs (see paragraphs 5, 7, and 19).

Nissen does not teach the specific coding sequence of the growth hormone gene.

GenBank Accession No. E01123 teaches the coding sequence of the hGH gene. This sequence exactly matches the instantly claimed SEQ ID NO: 1 (see alignment below).

```
LOCUS       E01123                  607 bp    RNA     linear   PAT 29-SEP-1997
DEFINITION  cDNA encoding human growth hormone derivatie.
ACCESSION   E01123
VERSION     E01123.1  GI:2169382
KEYWORDS    JP 1987048386-A/2.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Euarchontoglires; Primates; Catarrhini;
            Hominidae; Homo.
REFERENCE   1  (bases 1 to 607)
  AUTHORS   Sutanrei,R.J.J.J.
  TITLE     DEVELOPMENT VECTOR USED IN E. COLI
  JOURNAL   Patent: JP 1987048386-A 2 03-MAR-1987;
            ELI LILLY & CO
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COMMENT      OS    (human)
             PN    JP 1987048386-A/2
             PD    03-MAR-1987
             PF    26-AUG-1986 JP 1986201224
             PR    26-AUG-1985 US 85    769221
             PI    SUTANREI RICHIYAADO JIYASUKUNASU JIYUNIA
             PC    C12N15/00,C12N1/20,(C12N1/20,C12R1:19);
             CC    strandedness: Double;
             CC    topology: Linear;
             CC    hypothetical: No;
             CC    anti-sense: No;
             CC    *source: tissue_type=pituitaly;
             CC    *source: clone=pNM 1093;
             FH    Key              Location/Qualifiers
             FH
             FT    CDS              17. .595
             FT                     /product='human growth hormone derivatie' FT
             5'UTR             1. .16
             FT    3'UTR            596. .605
             FT    mRNA             1. .605.
FEATURES              Location/Qualifiers
   source           1. .607/organism="Homo sapiens"
                      /mol_type="genomic RNA"
                      /db_xref="taxon:9606"
ORIGIN

  Query Match             100.0%;  Score 573;  DB 2;  Length 607;
  Best Local Similarity   100.0%;  Pred. No. 2.6e-149;
 Matches  573;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 TTCCCAACCATTCCCTTATCCAGGCTTTTTGACAACGCTATGCTCCGCGCCCATCGTCTG 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         23 TTCCCAACCATTCCCTTATCCAGGCTTTTTGACAACGCTATGCTCCGCGCCCATCGTCTG 82

Qy         61 CACCAGCTGGCCTTTGACACCTACCAGGAGTTTGAAGAAGCCTATATCCCAAAGGAACAG 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         83 CACCAGCTGGCCTTTGACACCTACCAGGAGTTTGAAGAAGCCTATATCCCAAAGGAACAG 142

Qy        121 AAGTATTCATTCCTGCAGAACCCCCAGACCTCCCTCTGTTTCTCAGAGTCTATTCCGACA 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        143 AAGTATTCATTCCTGCAGAACCCCCAGACCTCCCTCTGTTTCTCAGAGTCTATTCCGACA 202

Qy        181 CCCTCCAACAGGGAGGAAACACAACAGAAATCCAACCTAGAGCTGCTCCGCATCTCCCTG 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        203 CCCTCCAACAGGGAGGAAACACAACAGAAATCCAACCTAGAGCTGCTCCGCATCTCCCTG 262

Qy        241 CTGCTCATCCAGTCGTGGCTGGAGCCCGTGCAGTTCCTCAGGAGTGTCTTCGCCAACAGC 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        263 CTGCTCATCCAGTCGTGGCTGGAGCCCGTGCAGTTCCTCAGGAGTGTCTTCGCCAACAGC 322

Qy        301 CTGGTGTACGGCGCCTCTGACAGCAACGTCTATGACCTCCTAAAGGACCTAGAGGAAGGC 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        323 CTGGTGTACGGCGCCTCTGACAGCAACGTCTATGACCTCCTAAAGGACCTAGAGGAAGGC 382
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Qy     361 ATCCAAACGCTGATGGGGAGGCTGGAAGATGGCAGCCCCCGGACTGGGCAGATCTTCAAG 420
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     383 ATCCAAACGCTGATGGGGAGGCTGGAAGATGGCAGCCCCCGGACTGGGCAGATCTTCAAG 442

Qy     421 CAGACCTACAGCAAGTTCGACACAAACTCACACAACGATGACGCACTACTCAAGAACTAC 480
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     443 CAGACCTACAGCAAGTTCGACACAAACTCACACAACGATGACGCACTACTCAAGAACTAC 502

Qy     481 GGGCTGCTCTACTGCTTCAGGAAGGACATGGACAAGGTCGAGACATTCCTGCGCATCGTG 540
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     503 GGGCTGCTCTACTGCTTCAGGAAGGACATGGACAAGGTCGAGACATTCCTGCGCATCGTG 562

Qy     541 CAGTGCCGCTCTGTGGAGGGCAGCTGTGGCTTC 573
           |||||||||||||||||||||||||||||||||
Db     563 CAGTGCCGCTCTGTGGAGGGCAGCTGTGGCTTC 595
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It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize the hGH coding sequence as the monomer in the multimeric constructs taught by either Elmorjani or Hallewell. Nissen taught that a useful method of increasing the half-life of injected cytokines (and thereby improving their therapeutic efficacy) was to increase the molecular weight of the protein via construction of a multimeric construct (see above). Although Nissen did not teach the specific growth hormone coding sequence, this sequence was well known in the art as evidenced by the GenBank sequence alignment presented above. The ordinary practitioner would have been motivated by the teachings of Nissen to construct multimer assemblies as taught by either Elmorjani or Hallewell using the hGH coding sequence as the monomer in order to obtain a construct capable of producing expression products (hGH multimeric proteins) with improved therapeutic efficacy. The ordinary practitioner would have expected a reasonable level of success in making multimeric constructs comprising multiple copies of the hGH coding sequence since Elmorjani and Hallewell separately taught a general method of making the constructs and the coding sequence was readily available. Therefore, the person of ordinary skill in the art, interested in obtaining a more therapeutically useful form of

hGH, would have been motivated to make multimeric constructs as taught by either Elmorjani or Hallewell, using the hGH coding sequence as the monomer, as suggested by Nissen, thus resulting in the instantly claimed invention.

8. Claim 171 is rejected under 35 U.S.C. 103(a) as being unpatentable over Elmorjani et al. (Biochemical and Biophysical Research Communications (1997) 239: 240-246) in view of Sambrook et al. (Molecular cloning: a laboratory manual (1989) by Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory, page 1.59).

Elmorjani taught a multimer assembly comprising multiple amplification cassettes comprising 5' and 3' restriction pairs, as discussed in greater detail above. The restriction pair taught by Elmorjani (StuI/SnaBI) is a ligation-compatible non-regenerable blunt end pair (see above and Figure 1).

Elmorjani does not teach a restriction pair site that comprises incompatible overhangs that are subsequently converted to ligation-compatible non-regenerable blunt ended sites via polymerase or nuclease treatment.

Sambrook teaches a general method of cloning where blunt-ended or sticky-ended (overhanging) fragments are ligated into a plasmid vector.

Regarding claim 171, Sambrook teaches that when it is impossible to find a suitable match between the restriction sites in a plasmid vector and those at the ends of a foreign (insert) DNA, DNA fragments with incompatible ends may be filled in using the Klenow fragment of DNA polymerase I (page 1.59). Sambrook states that this procedure "generates complementary termini from restriction sites that are otherwise incompatible, thus facilitating ligation of the

vector and foreign DNAs. Because partial filling eliminates the ability of the termini on the same molecule to pair with one another, the frequencies of circularization and self-oligomerization during the ligation reaction are also reduced (page 1.59)."

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Sambrook to the method of Elmorjani. Elmorjani taught production of a multimer assembly using a restriction pair containing ligation-compatible non-regenerable ends (see above). Since Sambrook taught that any pair of termini resulting from restriction digestion could be made ligation-compatible via polymerase treatment (page 1.59), the ordinary practitioner would have been motivated to apply this teaching when compatible ends such as those taught by Elmorjani were unavailable (for example, when making a different multimeric construct), thereby eliminating the need for the monomeric sequence to contain such a restriction pair and expanding the range of possible multimeric assemblies. Since the teachings of Sambrook were applicable to any pair of termini produced by restriction digestion the ordinary practitioner would have expected a reasonable level of success in applying these teachings to production of a multimer assembly using the method taught by Elmorjani. Therefore, the person of ordinary skill, interested in obtaining a multimeric assemblies using the method of Elmorjani in the absence of a ligation-compatible, non-regenerable blunt end restriction pair, would have been motivated to create compatible, non-rengenerable blunt ends as suggested by Sambrook, thus resulting in the instantly claimed invention.

*Conclusion*

No claims are currently allowable.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The following references are noted as references of interest: Lewis et al. (Protein Expression and Purification (1996) 7: 400-406; cited in IDS), Shen et al. (US 5,683,695 A), Sytkowski (US 6,242,570; cited in IDS), Verhoeyen (US 6,204,366 B1), and Peterson et al. (US 6,242,211 B1).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is (571) 272-8291. The examiner can normally be reached on M-F 7:30-5 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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